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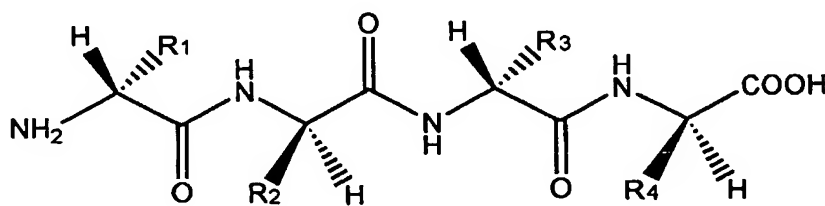
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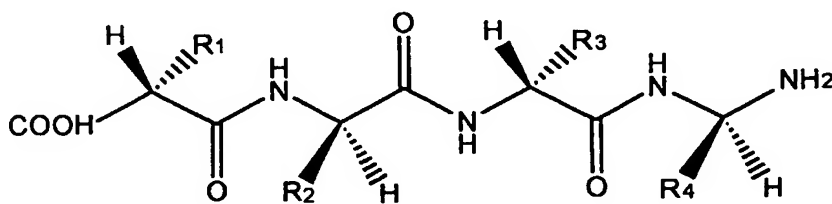
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(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING A RETRO-IVERSO ISOMER PETTIDE



I

(57) Abstract: The present invention provides a pharmaceutical composition comprising a peptide selected from the group consisting of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val, and D-Leu D-Thr D-Val as an active component. The composition of the present invention has great efficacy in lowering serum triglyceride levels.



II

WO 03/099315 A1

## A PHARMACEUTICAL COMPOSITION COMPRISING A RETRO-IVERSO ISOMER PEPTIDE

### Technical Field

5           The present invention relates to therapeutic peptides that possess inhibitory activity towards elevation of serum triglyceride (triacylglycerol) levels, an unavoidable result that occurs upon ingestion of meals containing high composition of fat. Administration of such peptides before or concomitantly with meals allows for less net absorption of fatty  
10 acids into the system, thereby contributing to the prevention of various known cardiovascular diseases as well as obesity-related ailments in general.

### Background Art

15           High serum triglyceride level, independent of the well-known risk factor of serum cholesterol, has been regarded as an additional risk factor for developing cardiovascular diseases, including coronary heart disease (Austin MA, *Am. J. epidemiol.* 129: 249-59,1989) and atherosclerosis (Patsch JR et al, *Arterioscler. Thromb.* 12: 1336-45,  
20 1992). A number of pharmaceutical developments have been made to restrict the elevation of serum triglyceride levels to prevent such cardiovascular ailments.

          More significantly, the excessive intake of lipid with respect to energy expenditure leads to obesity, which is currently being regarded as  
25 one of the prime health concerns in the Western World. Obesity is a complex medical disorder with implications for diabetes, high cholesterol, cardiovascular conditions, some forms of cancer, and is a major cause of premature mortality. Dietary restriction and behavioral changes are key to prevent obesity, however it is now becoming evident that the success  
30 in preventing or treating obesity can be increased with pharmaco-therapy. Several drugs have been developed to combat obesity, however most of

these are central-nervous system (CNS)-active, and hence have high abuse potential. Therefore, it would be desirable to have a pharmaceutical agent that would not have these dependency complications.

5           Recently, a group of low molecular weight peptides which were originally obtained and purified from a non-specific enzymatic proteolysate preparation of bovine reticulocyte protein has been shown to inhibit the elevation of serum triglyceride levels (US Patent 5,958,885). The peptides isolated are low molecular weight, i.e. 3-4 residues in  
10           length, and are comprised solely of natural amino acids.

          Now, retro-inverso technology, in which oligopeptides are synthesised that are similar to naturally occurring oligo-peptides but with mirror image amino acids put in reverse sequence order (Chorev M, Goodman M, TIBTECH 13:438-45, 1995), is a technology that has had  
15           limited take-up in recent years. By utilizing non-natural D-amino acids instead of L-amino acids, it can provide an advantage in bioavailability due to inherent resistance against various natural proteases *in vivo* but there is no expectation for its use to effectively mimic or better the biological action of naturally occurring peptides.

20

#### Disclosure of the Invention

          The present invention provides a pharmaceutical composition or a food composition for administration to a human or an animal comprising a retro-inverso isomer peptide as an active component.

25

#### Best mode for carrying out the Invention

          In one aspect of the present invention there is provided a pharmaceutical composition for administration to a human or an animal comprising , as an active component, a peptide selected from the group  
30           consisting of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val, and D-Leu D-Thr D-Val.

These peptides have unexpectedly been found to have a biological activity to reduce serum triglycerides. Among them, the peptides of D-Pro D-Tyr D-Val and D-Leu D-Thr D-Val substantially exceed the activity of the corresponding natural oligopeptide.

5 Unlike the natural oligopeptides, the peptides obtained from the retro-inverso chemical synthesis process are also available for functional group modifications, if required. This modification further allows for greater specificity and selectivity, and will also permit to tailor the activities of the peptides to suit the patient based on his/her intake of fat  
10 composition.

The peptide may, within the scope of the claimed invention, have minor modifications of a nature that is compatible with biological systems, suitably including phosphorylation; sulphonation or iodination of the D-Tyr and / or D-Thr. The D-Pro may, for example, be hydroxylated.  
15 Widely used automatic solid-phase peptide synthetic methods for performing the modification include N-alpha-acetylation or N-alpha-formylation for eliminating the positive charge of the N-terminus. When desiring to eliminate the negative charge on the C-terminus, a C-terminal carboxamide or alcohol ester can be readily generated by  
20 adopting standard solid-phase peptide synthetic resins.

For optimal activity, the peptide may be modified at the N or C, and suitably both, terminals of the peptide.

Complete reversal of ionization state can also be straightforwardly performed. The N-terminal NH<sub>2</sub> group is suitably replaced with a COOH  
25 group and the C-terminal COOH group is suitably replaced with an NH<sub>2</sub> group. This modification may suitably be undertaken using one of the conventional techniques for this purpose.

A route for this modification involves:

- 30 (1) a C-2 substituted malonyl (or malonamyl) residue substitution for the N-terminal retro-inverso peptide residue, and
- (2) a *gem*-diamino alkyl residue substitution for the C-terminal retro-inverso peptide residue.

The pharmaceutical composition is suitably provided in a form selected from the group consisting of a tablet, a powder, a granule, a pill and an injectable form. If provided in an injectable form it is suitably selected from the group consisting of a solution, a suspension and an emulsion.

The said injectable form may be administered by intravenous, intramuscular, subcutaneous, intracutaneous and intraperitoneal administration. The pharmaceutical composition suitably comprises from 1 to 100 mg of said peptide.

According to a second aspect of the invention there is suitably provided a food composition for administration to a human or an animal comprising a peptide consisting of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val, and D-Leu D-Thr D-Val as an active component.

The present invention is further illustrated and described by the following examples, which should not be taken to limit the scope of the invention.

#### Example 1. Chemical Synthesis and Purification of Peptides

Peptides of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val and D-Leu D-Thr D-Val were synthesized on an Applied Biosystems/Perkin-Elmer 432A Synergy Peptide Synthesizer using FastMoc cycles. The synthesis chemistry involves 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) / piperidine activation, and uses dimethylformamide (DMF) / N-methylpyrrolidine (NMP) / dimethylsulfoxide (DMSO) as the coupling solvent. Synergy Fmoc-Amide resin (Applied Biosystems/Perkin-Elmer) or Rink amide methylbenzhydrylamine (MBHA) resin (NOVAbiochem) was used for the solid-phase support. The constituting N- $\alpha$ -9-fluorenylmethoxycarbonyl (Fmoc) protected D-amino acids (N- $\alpha$ -Fmoc-D-proline, N- $\alpha$ -Fmoc-O-t-butyl-D-tyrosine, N- $\alpha$ -Fmoc-D-valine, N- $\alpha$ -Fmoc-D-leucine, N- $\alpha$ -Fmoc-O-t-butyl-D-threonine) were from

NOVABIOCHEM. The peptides were cleaved by adding 1.8 ml of trifluoroacetic acid (TFA) with 0.1 ml of 1,2-ethanedithiol (EDT) and 0.1 ml of thioanisole as scavengers for 1 hour, then precipitated with 15 ml of methyl tert-butyl ether (MTBE) at 4°C and centrifugation at 2000 xg. 5 The MTBE washing was repeated three more times, and the peptides were solubilized with 20% acetic acid. To use as reference compounds, L-Val-L-Val-L-Tyr-L-Pro, L-Val-L-Tyr-L-Pro, and L-Val-L-Thr-L-Leu peptides were prepared using the same methodology.

When necessary, purification of the peptides was performed using preparative reversed-phase HPLC. A Kromasil KR-100-10-C8 (10 mm x 250 mm, C8, 10 µm, 100 Å, Akzo Nobel) Column was used, with a linear gradient of 5 to 20% acetonitrile (CH<sub>3</sub>CN) in 0.1% TFA over 20 column volumes. The fractionated peak was checked for purity using a Vydac (Registered Trade Mark) 218TP52 RP-HPLC column (2.1 mm x 15 250 mm, C8, 5 µm, 300 Å) with a linear gradient of 1 to 25% CH<sub>3</sub>CN in 0.1% TFA. The final purity of each peptide was greater than 97%. MALDI-TOF mass spectrometry analyses using cinnapinic acid as matrix on a Kompact Research MALDI IV instrument (Kratos Analytical) confirmed the identities of the peptides.

20

Example 2. Oral Administration of Chemically Synthesised Peptides to Determine Inhibition of Triglyceride Level Elevation After Feeding

Olive oil (250 mg) was administered via gastric intubation to male 25 ICR mice (6-week old, body weight: 20 g), which were fasted overnight. The peptides were dissolved in 0.1 ml saline solution and administered orally one hour after lipid administration. For the control group, 0.1 ml of saline solution was administered per mouse. After two hours, blood was collected from the orbital vein under ether anesthesia and the serum 30 was separated by centrifugation (3000 rpm, 30 min, 1°C). Serum triglyceride levels were assayed using commercially available methods

(e.g. INFINITY (Registered Trade Mark) triglycerides reagent; Sigma Chemical Co.). The results were compared with L-Val-L-Val-L-Tyr-L-Pro (Reference Peptide 1), L-Val-L-Tyr-L-Pro (Reference Peptide 2), and L-Val-L-Thr-L-Leu (Reference Peptide 3) and shown in Table 1.

Table 1

	Peptide Dosage (mg / mouse)	Number of animal (n)	Serum Triglyceride (mg / 100 ml)	% Decrease
Distilled Water Only	-	5	92.2 ± 15.7	-
Olive Oil Only	-	24	376.2 ± 23.8	-
SEQ ID No. 1 (D-Pro D-Tyr D-Val D-Val C-NH <sub>2</sub> )	1.0	14	313.7 ± 45.9	22.0 %
Ref. Peptide 1 (L-Val L-Val L-Tyr L-Pro)	1.0	7	244.7 ± 25.5	46.3 %
SEQ ID No. 2 (D-Pro D-Tyr D-Val C-NH <sub>2</sub> )	1.0	7	231.8 ± 27.6	50.8 %
Ref. Peptide 2 (L-Val L-Tyr L-Pro)	1.0	14	407.7 ± 42.0	0 %
SEQ ID No. 3 (D-Leu D-Thr D-Val C-NH <sub>2</sub> )	1.0	7	294.6 ± 33.8	28.7 %
Ref. Peptide 3 (L-Val L-Thr L-Leu)	1.0	14	352.7 ± 35.6	8.3 %

In Table 1, "C-NH<sub>2</sub>" means that the C-terminal of a peptide has a carboxamide form.

As shown in Table 1, SEQ ID NO. 2 and SEQ ID NO. 3 display higher activities in lowering elevated serum triglyceride levels than Reference 2 and 3, respectively. SEQ ID NO. 1, although less active than Reference Peptide 1, nevertheless exhibits demonstrable serum

triglyceride lowering activity, its activity being about half of Reference Peptide 1. In general, it can be shown that for the three cases, there exist at least 20 % or greater statistically significant decrease in serum triglyceride levels, and for the cases of tripeptides, the retro-inverso compounds substantially exceed the activity of the corresponding natural oligo-peptides.

As noted previously, for enhanced efficacy the retro-inverso peptides suitably have modified N and C terminals, where the N-terminal of the retro-inverso peptide is converted to replace the NH<sub>2</sub> group with a COOH group and the C-terminal COOH group is replaced with an NH<sub>2</sub> group. This modification may be achieved by carrying out a C-2 substituted malonyl (or malonamyl) residue substitution for the N-terminal retro-inverso peptide residue (Residue R<sub>1</sub> in Fig. 1), and a *gem*-diamino alkyl residue substitution for the C-terminal retro-inverso peptide residue (Residue R<sub>4</sub>).

Figure 1 shows the structural differences between the retro-inverso peptide H-D-R<sub>1</sub>-D-R<sub>2</sub>-D-R<sub>3</sub>-D-R<sub>4</sub>-OH (Structure 1) and the end-group modified peptide HO-*m*R<sub>1</sub>-D-R<sub>2</sub>-D-R<sub>3</sub>-*g*R<sub>4</sub>-H (Structure II, where *m* and *g* denote malonyl and *gem*-diaminoalkyl residues, respectively).

Procedures to accomplish these end group modifications are well-documented, and are reviewed in Fletcher MD, Campbell MM, Chem Rev 1998, 98: 763-795 and Chorev M, Goodman, Acc Chem Res 1993, 26:266-73.

According to the present invention, it becomes possible to prevent hyperlipemia in human and domestic animals upon administration of the peptides found in the sequence listing. Such treatment is now known to have far reaching benefits, including but not restricted to, cardiovascular ailments such as hypertension and arteriosclerosis, and obesity-related complications in general.

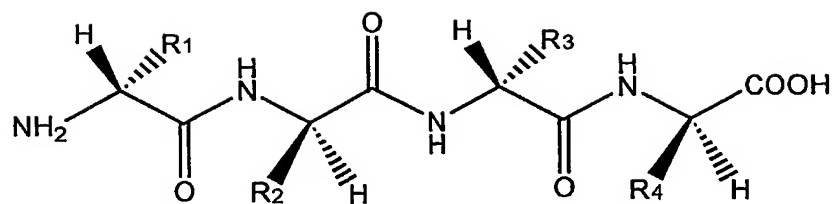


What is claimed is:

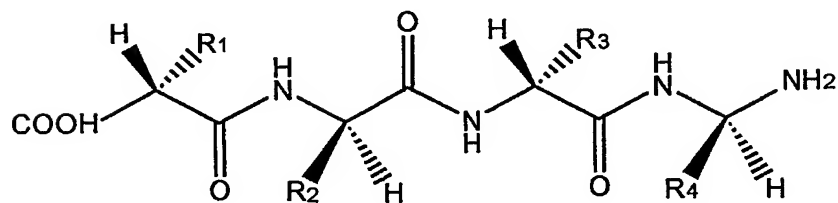
1. A pharmaceutical composition for administration to a human or an animal comprising a peptide selected from the group consisting of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val, and D-Leu D-Thr D-Val as an active component.  
5
2. The pharmaceutical composition of claim 1, being selected from the group consisting of a tablet, a powder, a granule, a pill and an injectable form.  
10
3. The pharmaceutical composition of claim 2, which is an injectable form.
4. The pharmaceutical composition of claim 3, wherein said injectable form is selected from the group consisting of a solution, a suspension and a emulsion.  
15
5. The pharmaceutical composition of claim 1, wherein the composition comprises from 1 to 100 mg of said peptide.  
20
6. A pharmaceutical composition as claimed in any of claims 1 to 5, wherein the N-terminal NH<sub>2</sub> group is replaced with a COOH group and/or the C-terminal COOH group is replaced with an NH<sub>2</sub> group.
7. A food composition for administration to a human or an animal comprising a peptide selected from the group consisting of D-Pro D-Tyr D-Val D-Val or D-Pro D-Tyr D-Val or D-Leu D-Thr D-Val as an active component.  
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1/1

FIG. 1





I



II

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR03/01017

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> <b>IPC7 A61K 38/04</b> According to International Patent Classification (IPC) or to both national classification and IPC				
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC7 A61K 38/04, A61K 38/07, A23L 1/305, A23K 1/16, C07K 5/103 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Korean Patents and applications for inventions since 1975 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN, PUBMED, DELPHION, KISTI				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	WO 97/00890 A1 (ITOHAM FOODS INC.) 09 JANUARY 1997 see the whole document	1-7		
Y	EP 0838473 A1 (HANKYU KYOEI BUSSAN CO., LTD.) 29 APRIL 1998 see the page1 line5 - page5 line3 page7 line34 - page8 line54 page1 line5 - page5 line3 all claims	1-7		
Y	WO 8906970 A1 (HANKYU KYOEI BUSSAN CO., LTD.) 10 AUGUST 1989 see the whole document	1-7		
A	US 5756467 (HANKYU KYOEI BUSSAN CO., LTD.) 26 MAY 1998 see the whole document	1-7		
A	JP 11263733 A2 (HANKYU KYOEI BUSSAN CO., LTD.) 28 SEPTEMBER 1999	1-7		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; border: none;">           * Special categories of cited documents:            "A" document defining the general state of the art which is not considered to be of particular relevance            "E" earlier application or patent but published on or after the international filing date            "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)            "O" document referring to an oral disclosure, use, exhibition or other means            "P" document published prior to the international filing date but later than the priority date claimed         </td> <td style="width: 50%; vertical-align: top; border: none;">           "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention            "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone            "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art            "&amp;" document member of the same patent family         </td> </tr> </table>			* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search 26 AUGUST 2003 (26.08.2003)		Date of mailing of the international search report 27 AUGUST 2003 (27.08.2003)		
Name and mailing address of the ISA/KR  Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140		Authorized officer CHO, Hee Won Telephone No. 82-42-481-5607 		

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR03/01017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 97/00890 A1	06.07.2000	US 6046168	04.04.2000
		PT 0753526 T	29.06.2001
		NO 0976042 A0	22.12.1997
		KR 0262468 B1	01.08.2000
		JP 6293796 A2	21.10.1994
		GR 3035607 T3	29.06.2001
		FI 0974601 A0	22.12.1997
		ES 2153415 T3	01.03.2001
		EP 0838474 A4	18.04.2001
		DK 0753526 T3	05.03.2001
		CA 2225412 C	20.02.2001
		DE 69426465 T2	07.06.2001
		AU 6115494 A1	11.10.1994
EP 0838473 A1	29.04.19989	US 5958885	28.09.1999
		KR 0264344 B1	01.08.2000
		JP 9255698 A2	30.09.1997
		DK 0838473 T3	17.02.2003
		CA 222176 C	23.01.2001
		AU 5912096 A1	17.10.1997
		AT 0225803	15.10.2002
WO 8906970 A1	10.08.1989	US 5723443	03.03.1998
		NO 0893882 A0	29.09.1989
		JP 5087052 B4	15.12.1993
		FI 0894619 A0	29.09.1989
		EP 0420979 B1	19.01.1994
		DK 0481589 A0	29.09.1989
		DE 68912589 T2	26.05.1994
		CA 1335567 A1	16.05.1995
		AU 3037089 A1	25.08.1989
US 5756467	26.05.1998	WO 9421671 A1	29.09.1994
		US 6046168	04.04.2000
		KR 016174 B1	16.11.1998
		EP 0753526 B1	20.12.2000
		CA 2158991 C	20.02.2001
JP 11263733 A2	28.09.1999	JP 3108675 B2	13.11.2000

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## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 A61K 38/04, A61K 38/07, A23L 1/305, A23K 1/16, C07K 5/103

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5756467 (HANKYU KYOEI BUSSAN CO., LTD.) 26 MAY 1998 see the whole document	1-7
A	JP 11263733 A2 (HANKYU KYOEI BUSSAN CO., LTD.) 28 SEPTEMBER 1999	1-7

☐ Further documents are listed in the continuation of Box C.

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"&" document member of the same patent family

Date of the actual completion of the international search

26 AUGUST 2003 (26.08.2003)

Date of mailing of the international search report

27 AUGUST 2003 (27.08.2003)

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CHO, Hee Won

Telephone No. 82-42-481-5607



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR03/01017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 97/00890 A1	06.07.2000	US 6046168	04.04.2000
		PT 0753526 T	29.06.2001
		NO 0976042 A0	22.12.1997
		KR 0262468 B1	01.08.2000
		JP 6293796 A2	21.10.1994
		GR 3035607 T3	29.06.2001
		FI 0974601 A0	22.12.1997
		ES 2153415 T3	01.03.2001
		EP 0838474 A4	18.04.2001
		DK 0753526 T3	05.03.2001
		CA 2225412 C	20.02.2001
		DE 69426465 T2	07.06.2001
		AU 6115494 A1	11.10.1994
EP 0838473 A1	29.04.19989	US 5958885	28.09.1999
		KR 0264344 B1	01.08.2000
		JP 9255698 A2	30.09.1997
		DK 0838473 T3	17.02.2003
		CA 222176 C	23.01.2001
		AU 5912096 A1	17.10.1997
		AT 0225803	15.10.2002
WO 8906970 A1	10.08.1989	US 5723443	03.03.1998
		NO 0893882 A0	29.09.1989
		JP 5087052 B4	15.12.1993
		FI 0894619 A0	29.09.1989
		EP 0420979 B1	19.01.1994
		DK 0481589 A0	29.09.1989
		DE 68912589 T2	26.05.1994
		CA 1335567 A1	16.05.1995
		AU 3037089 A1	25.08.1989
US 5756467	26.05.1998	WO 9421671 A1	29.09.1994
		US 6046168	04.04.2000
		KR 016174 B1	16.11.1998
		EP 0753526 B1	20.12.2000
		CA 2158991 C	20.02.2001
JP 11263733 A2	28.09.1999	JP 3108675 B2	13.11.2000